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THEORETICAL REVIEW

A fresh look at the use of nonparametric analysis in actimetry

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SUMMARY

Actimetry has been used to estimate the sleep–wake cycle instead of the rest-activity rhythm. Although algorithms for assessing sleep from actimetry data exist, it is useful to analyze the rest-activity rhythm using nonparametric methods. This would then allow rest-activity rhythm stability, fragmentation and amplitude to be quantified. In addition, sleep and wakefulness efficiency can be quantified separately. These variables have been used in studies analyzing the effect of age, diseases and their respective treatments on human circadian rhythmicity. In this study, we carried out a comprehensive analysis of the main results from published articles and devised a functional model of interaction among the several components involved in generating the sleep–wake cycle. The nonparametric variables render it possible to infer the main characteristics of circadian rhythms, such as synchronization with a zeitgeber, and its amplitude and robustness.

Introduction

Actimetry has been a focus of the fields of sleep research and sleep medicine. The proportion of studies published involving actimetry related to polysomnography has increased from 1:10 to 1:4 in less than 20 y [1]. Besides sleep assessment, actimetry has also been used to register the rest-activity rhythm. The most widely used method to characterize the rest-activity rhythm, the cosinor method, is based on parameters of a known function, the cosine [2]. When the cosinor method is applied, a mathematical model fits the data to a cosine curve. Information about the rhythm is then extracted from this fitted curve, such as acrophase, mesor, period and amplitude. Thus, the adjustment of a cosine function in relation to a rest-activity record provides parameters that are used in the study of circadian rhythmicity. These variables are called parametric [3]. In some cases, the time series of a biological rhythm follows a sinusoidal function and the cosinor method is indicated to analyze such rhythms. The rhythm of body temperature is a good example of this, although not all biological rhythms follow this pattern.

The rest-activity rhythm is a biological rhythm that does not follow a sinusoidal waveform. For this reason other variables have been proposed to describe this rhythm more adequately [4,5]. Since some variables generated by these methods are not related to the parameters obtained by adjustment to the cosine function, they are referred to as nonparametric functions. These variables include: intradaily variability (IV), interdaily stability (IS), the least active five-hour period (L5) and the most active ten-hour period (M10). In contrast to cosinor, this methodology does not follow the assumption that the rest-activity rhythm behaves similarly to a sinusoidal wave.

The intradaily variability (IV) provides information on rest-activity rhythm fragmentation. Its calculation is based on the first derivate of the hourly clustered actimetry data (Equation (1)). The first derivate is the result of subtracting the previous element (X_{i-1}) from the posterior element (X_i) of the raw data. From the first derivate, the root mean square is calculated $\sum_{i=2}^{N}(X_i - X_{i-1})^2/(N-1)$ and the result normalized by the raw data

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Glossary of terms

ADHD	attention-deficit/hyperactivity disorder
AMP	amplitude
CNS	central nervous system
CSDD	Cornell scale for depression in dementia
CTS	circadian timing system
CVD	cardiovascular disease
DWMH	deep white matter hyperintensities
FAST	functional assessment staging scale
IS	interdaily stability
IV	intradaily variability
L5	least active five-hour period
L5m	mean of least active five-hour period
L5mp	least active five-hour period in mean profile
M10	most active ten-hour period
M10m	mean of most active ten-hour period
M10mp	most active ten-hour period in mean profile
MMSE	mini-mental state examination test
MOSES	multidimensional observation scale for elderly subjects
NI-ADL	nurse informant index of activities of daily living
PSQI	Pittsburgh sleep quality index
PVH	periventricular hyperintensities
RA	relative amplitude
RAm	mean of relative amplitude
RAmp	relative amplitude in mean profile
RHT	retinohypothalamic tract system
SAD	seasonal affective disorder
SCN	suprachiasmatic nucleus
TENS	transcutaneous electrical nerve stimulation
UPDRS	unified Parkinson's disease rating scale
VIP	vasoactive intestinal polypeptide

population variance $(\sum_{i=1}^{N}(X_m - X_i)^2)/N$. Large hourly differences such as daytime sleep or nighttime awakenings increase the value of IV.

$$\mathrm{IV} = \frac{\sum_{i=2}^{N}(X_i - X_{i-1})^2 N}{(N-1)\sum_{i=1}^{N}(X_i - X_m)^2} \quad (1)$$

Interdaily stability (IS), which yields information about the rest-activity rhythm synchronization with the light–dark cycle, is calculated from the mean 24-h profile (24 points represent the hours of the day). In Equation (2), N corresponds to the total number of data items, p is the number of data items per day (24 in this case), X_m is the average of all data, X_h corresponds to each hour of the mean profile, while X_i represents each given hour of raw data. IS is calculated as the variance of the average daily profile divided by the total variance.

$$\mathrm{IS} = \frac{\sum_{h=1}^{p}(X_h - X_m)^2 N}{(p)\sum_{i=1}^{N}(X_i - X_m)^2} \quad (2)$$

Nocturnal activity, measured by the nonparametric variable 'L5', reflects the mean activity of the least active consecutive five hours of the day. Diurnal activity, measured by the nonparametric variable 'M10', reflects the mean activity of the most active ten hours of the day. Higher M10 values are found in people with an active lifestyle.

The calculation of the difference between nighttime and daytime activity yields values that show the amplitude of the rest-activity rhythm. Lower amplitude values are often found in individuals with medical conditions, for example in Alzheimer disease patients. It can therefore be assumed that the higher the amplitude values, the healthier the individual [4]. Depending on how the difference between M10 and L5 is calculated, we will have values for the absolute or relative amplitude of the rhythm. This point will be discussed in more detail in the ensuing section.

When compared to the parameters of a cosine function fitted to the data, the nonparametric values are found to be more efficient at identifying alterations in the rest-activity rhythm [3]. In this review, we present the use of nonparametric variables from actimetry using three study categories: those that compare individuals of different ages and with different neurodegenerative diseases compared to healthy control groups (Table 1); those that make associations between the nonparametric variables and other measures, such as quality of life (Table 2); and those that analyze the effect of interventions on individuals' routines, such as exposure to light, physical activities, etc. (Table 3).

Intradaily variability (IV)

One of the main drawbacks of the cosinor method is its inability to detect fragmentation in the rest-activity rhythm. This fragmentation may be derived from major alterations in the rest-activity rhythm, such as daytime sleepiness and/or nocturnal arousals. These alterations reflect the effect of age and central nervous system diseases on the sleep–wake cycle [6].

During ontogenesis, consolidation of the rest-activity rhythm occurs during the first mo of life, with a reduction in this rhythm fragmentation (Table 1) [3]. A study carried out with actimetry identified a lower intradaily variability at six mo of age than at 15 d of life [3]. This consolidation of the rest-activity rhythm stems from the maturation of the circadian timing system (CTS).

Huang et al. studied subjects from 20 to 92 y old and showed that the older adults displayed higher IV values, i.e., greater rhythm fragmentation and worse sleep efficiency (Table 1) [6]. CTS functionality depends on the integrity of its neurons from the suprachiasmatic nucleus (SCN) and of its projections into hypothalamic regions. It has been demonstrated that the number of vasoactive intestinal polypeptide (VIP) expressing neurons in the SCN is lower in the elderly, causing a reduction in coupling among the neural oscillators and a deficit in the circadian process [3,7–9]. This reduces the phase relation among the neural oscillators, decreasing the power of induction of the sleep and wakefulness phases (Fig. 1).

Besides the neuron degeneration that occurs naturally during the ageing process, disorders of the central nervous system (CNS), such as Alzheimer's, may accelerate this process, leading to a reduction in the number of peptide-expressing neurons in the SCN as well as in other cerebral regions [7,9]. This directly influences the rest-activity rhythm profile in this group. Witting et al. (1990) found a higher IV value for Alzheimer patients than for control subjects (Table 1) [4]. Hatfield et al. (2004) stratified Alzheimer patients into two groups according to disease stage, mild or moderate, and compared them to controls. Only the moderate Alzheimer group showed a higher intradaily variability than the control group (Table 1) [10].

A fragmented rhythm is related to degeneration in the CTS and influences the individual's quality of life. This can be exemplified by the finding of a negative correlation between IV and health indicator parameters (Fig. 2). For example, higher IV values were

Table 1
Studies using the nonparametric variables of actigraphy to compare different groups.

Authors	Groups	Comparison	
Harper et al. 2004 [24]	Control (C) Alzheimer disease (AD) Lewy body dementia (LBD)	**IS** **IV** **M10**	NS NS AD < C* LBD < AD*
		L5 **RA**	AD > C* NS
Witting et al. 1990 [3]	Young controls (YC) Old controls (OC) AD patients (AD) AD sedative users (SU) AD nonusers (NU)	**IS** **IV** **M10**	NS AD > OC* NU > OC* AD < OC** SU < OC*
		L5	NS
Van Someren et al. 1996 [4]	Controls (C) Presenile in home (PH) Senile in home (SH) Senile in institution (SI)	**IS** **IV** **M10**	SI <all other groups* NS SI<all other groups*
		L5	NS
Hatfield et al. 2004 [10]	Control (C) Mild AD (MiAD) Moderate AD (MoAD)	**IS** **IV** **M10** **L5** **RA**	MoAD < C* MoAD > C* MoAD < C* NS MoAD < C
Anderson et al. 2009 [27]	Controls (C) Frontotemporal dementia (FTD) FTD with normal MRI (FTDN) FTD with anormal MRI (FTDA)	**IS** **IV** **M10** **L5**	NS NS NS NS
Huang et al. 2002 [6]	Young (Y) Middle-age (MA) Old (O) Oldest (OST)	**IS** **IV** **L5**	NS OST > Y*** OST > MA*** O > Y*** O > MA*** OST > Y** OST > MA** O > Y** O > MA**
Zorzona-Moreno et al. 2011 [5]	15 days (15 d) 1 month (1 m) 3 months (3 m) 6 months (6 m)	**IS** **IV** **M10** **RA**	6 m > 3 m* 6 m > 1 m* 6 m > 15 d* 6 m < 3 m* 6 m < 1 m* 6 m < 15 d* NS 6 m > 1 m* 6 m > 15 d* 3 m > 1 m* 3 m > 15 d*
Jones et al. 2005 [18]	Control (C) Bipolar disorder (BD)	**IS** **IV**	C > BD* BD > C*
Whitehead et al. 2008 [19]	Control (C) Parkinson's disease (PD) PD patients without hallucinations (PDnH) PD patients with hallucinations (PDH)	**IS** **IV** **L5** **RA**	PDnH > PDH PD > C PDnH < PDH PDnH > PDH
Hare et al. 2006 [20]	Neurotypical adults (C) Adults with Asperger syndrome (AS)	**IS** **IV** **RA**	C > AS** NS C > AS***
Berle et al. 2010 [35]	Control (C) Depression (D) Schizophrenia (S) Schizophrenia + clozapine (S + C) Schizophrenia + other antipsychotics (S + OA)	**IS** **IV** **RA**	C > D* C < S* C < S + C** C > D* C > S* C > S + C** NS
Song et al. 2009 [32]	Institution for profit (A) Institution not for profit (B)	**IS** **IV** **L5** **RA**	A < B NS A > B A < B
Van der Heijden et al. 2005 [36]	Children with ADHD-noSOI Children with ADHD-SOI	**IS** **IV**	NS NS
Van Veen et al. 2010 [31]	Adult control (C) Adult with ADHD-noSOI (AnS) Adult with ADHD-SOI (AS)	**L5** **IS** **IV** **AMP**	NS C < AnS** AS < AnS*** C < ADHD* C > ADHD*** C > AS*** AS < AnS**

ADHD = attention-deficit/hyperactivity disorder, AMP = amplitude, IS = interdaily stability, IV = intradaily variability, L5 = least active five-hour period, M10 = most active ten-hour period, NS = not significant, RA = relative amplitude; SOI = sleep onset insomnia; (*) $p < =0.05$, (**) $p \leq 0.01$ and (***) $p \leq 0.001$.

correlated with worse sleep quality [11], lower amplitude for rest-activity rhythm [4,5], and poorer cognitive and motor performance, besides reduced social interaction (Table 2) [11,12].

The IV variable has also been used for the assessment of therapeutic strategies, such as exposure to bright light and physical exercise programs (Table 3) [14,15]. The effect of bright-light therapy for two hours a day in lowering rest-activity rhythm fragmentation among patients with dementia was detected by the reduction observed in IV values [14]. IV values were also found to be lower in healthy elderly after practicing physical activities for three mo, demonstrating a reduction in rest-activity rhythm fragmentation [15]. The authors suggested that this reduction was mainly related to the effect of exercise on sleep structure, and that the reduction of IV values represented sleep consolidation.

Interdaily stability (IS)

High IS values indicate that the subject is synchronized with the 24-h zeitgeber. This reflects good functioning of the CTS components related to photic and nonphotic synchronization (social effects, somatosensory input and physical activity) [4,5,15,32,33]. This synchronization may be influenced by age, mental disorders and lifestyle (Table 2) [6,16,17].

With regard to age, synchronization with zeitgeber improves as the circadian timing system matures, where six-month-old infants showed a higher IS value than 15-d-old newborns (Table 1) [5]. In another study, which divided volunteers according to age into four groups (young, middle-aged, old, and oldest subjects), no difference was found [6].

Patients with bipolar disorder had a less stable (smaller IS) and more fragmented (larger IV) rest-activity rhythm than subjects from a control group (Table 1) [18]. Patients with Parkinson's disease showed no difference in IS [19]. However, when patients were divided into two groups, with and without hallucinations, the authors observed that nonhallucinators showed more elevated IS than patients with hallucinations. Patients with Asperger's syndrome showed lower synchronization (<IS) with the external environment [20]. The researchers suggested that social factors may have played a role in this difference. In blind individuals, social cues were sufficient to maintain a synchronization cycle of 24 h, or higher IS [21].

Nurses working alternating shifts showed a lower level of rest-activity rhythm synchronization with the light–dark cycle than those who had a fixed day shift [22]. For those who worked only during the day, the IS average was 0.66, whereas for the alternating shift group the average was 0.25. Improved synchronization may be achieved through changes in daily routine, such as increasing the intensity of light during the day. An increase in light intensity elevated the IS values of Alzheimer patients [5]. The IS variable was shown to be more effective than cosinor for detecting increases in synchronization after the use of bright light.

Table 2
Methods nonparametric variables that correlate with other variables obtained in their studies.

Authors	Groups characteristics	IS	IV	M10	L5	RA
Witting et al. 1990 [3]	Age: 29–86 y *N*: 31 Young and old controls and old patients with Alzheimer	−IV*** +M10*** −L5**	−M10***			
Van Someren et al. 1996 [4]	Group of 34 patients with Alzheimer's disease, including presenile and senile patients living at home or in a nursing home, as well as in 11 healthy controls.	+M10*** +Senile onset* +Light exposure*	−M10*** +MMSE**			
Bromundt et al. 2011 [11]	Age: 28–56 y *N*: 14	−PSQI*	+PSQI* +Mean nap time**			+Sleep efficiency* −Fragmentation index* −PSQI** −Mean nap time**
Oosterman et al. 2009 [17]	Age: 69.5 ± 8.5 y *N*: 144 IQ of 98.9 ± 13.4 MMSE of 27.9 ± 1.6 7 d of actigraphy recording		−Mental speed*** −Memory*** −Executive function***			+Mental speed** +Memory* +Executive function***
Harper et al. 2008 [37]	Male patients ($n = 19$) residing at the E. N. Rogers Memorial (ENRM) Veterans Administration (VA)		−Vasopressin***		−Neurotensin*	+Neurotensin***
Oosterman et al. 2008 [12]	Participants were recruited in cooperation with the Sint Lucas Andreas Hospital in Amsterdam. $N = 135$. A minimum of 5 d of actigraphy recording	−Occiptal PVH* −Frontal DWMH* (frontal DWMH was the sole predictor of IS)*	(Age entered as a significant predictor of IV)*	(Frontal DWMH predicted M10)**		−Occiptal PVH* −Frontal DWMH** (frontal DWMH was the only significant predictor of AMP)*
Whitehead et al. 2008 [19]	Participants: 31 healthy older adults and 77 patients diagnosed with idipathic PD	+UPDRS-IV*	+Age*			+MMSE* −UPDRS-III* −UPDRS 21*
Carvalho-Bos et al. 2007 [13]	Eighty-seven women aged 85.5 ± 5.9 y (mean ± standard deviation) were studied while living in assisted care facilities at 12 different homes for the elderly in The Netherlands	+MMSE* −FAST*** −NI-ADL*** −CSDD*** −MOSES***	+FAST* +NI-ADL** +CSDD* +MOSES*	−FAST*** −NI-ADL*** −CSDD*** −MOSES***	−FAST*** −NI-ADL*** −CSDD*** −MOSES***	−FAST* −CSDD* −MOSES**

(+) and (−) indicates respectively a positive and a negative relation between variables, AMP = amplitude, CSDD = Cornell scale for depression in dementia, DWMH = deep white matter hyperintensities, FAST = functional assessment staging scale, IS = interdaily stability, IV = intradaily variability, L5 = least active five-hour period, MMSE = mini-mental state examination test, MOSES = multidimensional observation scale for elderly subjects, M10 = most active ten-hour period, NI-ADL = nurse informant index of activities of daily living, NI-NS = not significant, PD = Parkinson's disease, PSQI = Pittsburgh sleep quality index, PVH = periventricular hyperintensities, RA = relative amplitude, UPDRS = unified Parkinson's disease rating scale; (*) $p \leq 0.05$, (**) $p \leq 0.01$ and (***) $p \leq 0.001$.

Exposure to light and the input of this information to the SCN are responsible for synchronizing photic cues (Fig. 1). Alzheimer patients were less exposed to natural light than the control individuals [24]. Furthermore, these patients have retina and optic nerve degeneration [25]. Van Someren et al. (1996) divided an Alzheimer patient group according to age at disease onset: before (pre-senile) or after (senile) 65 y of age; and to place of abode: in their homes or in institutions [4]. The study showed that synchronization with natural light/dark was weaker in senile institutionalized patients [4]. Hatfield studied a group of patients that lived in their homes with caregivers, stratifying these subjects into mild and moderate Alzheimer's disease [10]. Compared to a control group, the patients with moderate disease showed a less synchronized rhythm, i.e., exhibited lower IS values [10]. Synchronization increased with somatosensory stimuli applied through transcutaneous stimulation [33].

Rhythm stability, as measured by IS, seems to show a direct relationship with quality of life measurements (Fig. 2). Patients with a higher synchronization rate (IS) showed a larger amount of daytime activity measured by M10 and a lower amount of nocturnal activity measured by L5 (Table 2) [4,5]. Elderly women with dementia and a high IS rate showed more preserved cognitive function [13]. In a study of schizophrenic patients, those with higher IS showed lower daytime sleepiness levels [11].

Least active five-hour period or nocturnal activity (L5)

A nonparametric variable for measuring rest phase is obtained by averaging the sum of activities during the least active five-hour period (L5). A low value of L5 indicates sleeping with few arousals and a less fragmented rhythm (Fig. 1). As previously discussed for IV, the degeneration of the circadian timing system as a result of ageing may increase L5 values [6]. This is evidenced by an inverse correlation between L5 and the neuronal expression of neurotensin in the SCN (Table 2). Alzheimer patients showed more intense nocturnal activity than control subjects [24]. Parkinson patients displayed sleep fragmentation while those with hallucinations had a higher L5 value than those without hallucinations [19].

The first L5 description stated that "L5 were computed by averaging the 5 lowest hourly means" and "L5 represents movement-activity during sleep plus nighttime arousals" [4]. Since there is no explicit description, we believe that this value was calculated based on the whole record, which in the cited study was from 3.75 to 7 d. In this case, if the individual is under the effect of medication or has been sleep deprived on one of the registered days, the L5 value may be masked. Therefore, we propose calculating this value for each day.

Other studies calculated the L5 value based on the mean profile, thus, the lower the L5 value, the more regular the rest [6,14,25]. In a

Table 3
Studies using interventions to alter the circadian rhythms.

Authors	Groups	Treatment duration (days)/description	Comparison	
Van Someren et al. 1997 [14]	Baseline 1 (B1) Treatment (T) Baseline 2 (B2)	4/light intensity was 1136 ± 89 lux 2 h/d	**IS** **IV**	T > B1** T < B1**
Sloane et al. 2007 [34]	Light morning LM (07:00–11:00 h) Light evening LE (16:00–20:00 h) Light all-day LAD (07:00 h–20:00 h)	21/light intensity was 2495 ± 179 lux in NC and 2641 ± 259 in OR	**IS** **IV** **M10** **L5** **RA**	NS NS NS NS NS
Scherder et al. 1999 [33]	Pooled baseline (PB) Treatment (T)	Electrostimulator on two electrodes placed on patient's back between Th1 and Th5	**IS** **IV** **RA**	T > PB** NS NS
Van Someren et al. 1997 [15]	Pre Post Follow-up	Supervised indoor aerobic activities for 3 mo, three times 1.5 h a week, at around noon.	**IS** **IV** **RA**	NS Pre > Post NS
Winkler et al. 2005 [38]	Control (C) Seasonal affective disorder (SAD)	28/10,000 lux for 1.5 h between 07:00 h–09:00 h	**RA**	SAD < C

IS = interdaily stability, IV = intradaily variability, L5 = least active five-hour period, M10 = most active ten-hour period, NC = North Caroline, NS = not significant, OC = Oregon city, RA = relative amplitude; $p < =0.05$, (**) $p \leq 0.01$ and (***) $p \leq 0.001$.

situation in which the subject has efficient rest yet with irregular sleep episodes (free-running, for example), their L5 value will be high. Thus, we propose that the L5 value should be calculated in two ways: for each day (L5m) and based on the 24-h mean profile (L5mp). In the first case, the information will be related to rest quality, and in the second, to rest regularity. Consequently, this gives rise to two new distinct variables, L5m and L5mp.

Most active ten-hour period or daytime activity (M10)

Reduced rest-activity rhythm amplitude may be related to a reduction in motor capacity or to difficulty of the CTS in adjusting activity during a given phase (Fig. 1). Thus, low M10 values are expected to be associated with motor difficulty, exercise reduction or CTS degeneration (Table 2).

The M10 value in institutionalized patients with Alzheimer's was found to be lower than in both controls and patients living at home [4]. Alzheimer patients at a later stage with Lewy bodies had reduced daily activity compared to individuals without Lewy bodies [24]. Patients at a milder stage of the disease displayed no difference in this variable compared with a control group [10]. However, when the disease is more severe, there is a significant decline in daily activities. Thus, it follows that higher M10 values are associated with better quality of life.

Correlation and regression analyses indicate an association between rhythm amplitude and cortical function (see Table 2) [12,13]. The integrity of the frontal cortex influences the M10 value [12]. Performance on cognitive, functional, behavioral and emotional activities is worse in patients with a low M10 value [13].

The discussion over L5 regarding its daily calculation and the average 24-h profile is also valid for M10. For this reason, we also suggest that M10 be calculated in two ways: for each day (M10m)

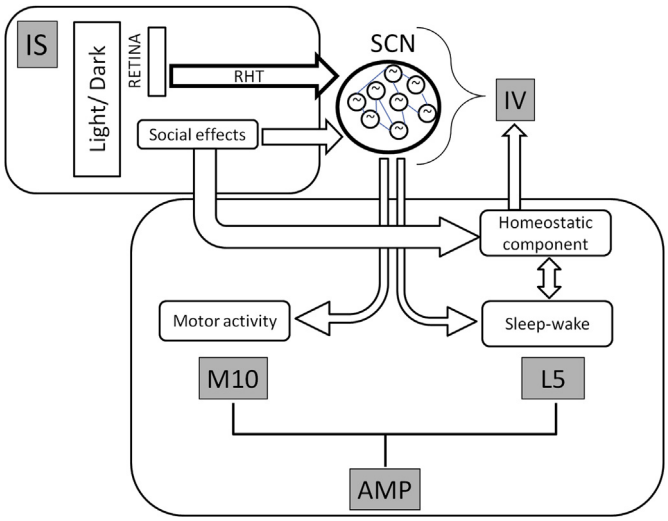

Fig. 1. Relationship between the circadian timing system, the rest-activity rhythm and nonparametric variables. Synchronization with the external world is measured by IS, which is related to the inputs to the main circadian oscillator (SCN) synchronized by the light–dark cycle. The degeneration of this oscillator affects mainly rhythm fragmentation, as measured by IV, and its output amplitude (Amp). When synchronization weakens, there is a reduction in motor activity, measured by M10, and sleep–wake cycle fragmentation. This is accompanied by an increase in L5 values, which reflects activity during rest. On the other hand, a reduction of motor activity and in SCN control over the motor system causes a decrease in the M10 value. SCN: suprachiasmatic nucleus. RHT: retinohypothalamic tract, IS: interdaily stability, IV: intradaily variability, M10: most active ten-hour period, L5: least active five-hour period.

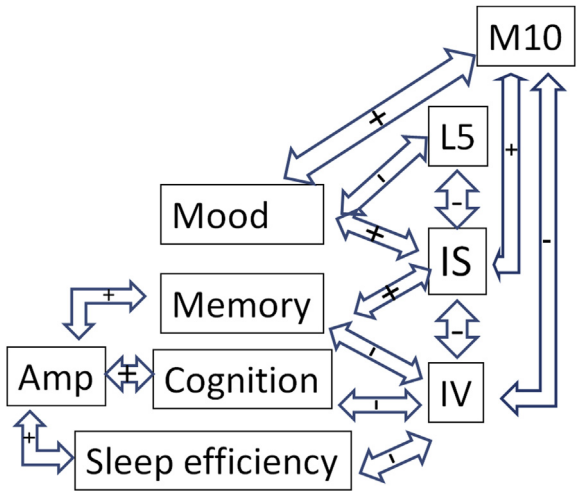

Fig. 2. Correlations between nonparametric variables and neurobehavioral functioning. A rhythm that is well synchronized with the light/dark cycle is associated with improvements in mood and memory as well as an increase in amplitude of the rest-activity rhythm. Rhythm fragmentation calculated by IV is associated with impairment in cognition, memory, sleep efficiency and synchronization with the external light/dark cycle. IV: intradaily variability. AMP, amplitude, IS, interdaily stability, L5, least active five-hour period, M10, most active ten-hour period.

and for the average 24-h profile (M10mp). In the first case, the information relates to daily activity intensity, while the second reflects activity regularity.

Rhythm amplitude

Different formulas are used to calculate rhythm amplitude (AMP) from M10 and L5 variables. According to Witting et al., the difference between M10 and L5 yields no further information beyond the M10 value [3]. Therefore, the group limited the use of M10 to an appropriate amplitude approximation.

In another study, this variable, called AMP, was calculated as the difference between M10 and L5, both variables however, were obtained from the 24-h mean profile [6,14,17]. In this case, the calculated AMP value was not normalized, and likewise for M10 and L5. Another variable was therefore created, relative amplitude (RA). This was calculated as the difference between M10 and L5 divided by M10 + L5 [3,13,23,26]. In this case, RA was calculated considering the average 24-h profile. Another approach for normalizing amplitude involves dividing the difference between M10 and L5 by the average for each day [27].

Relative rhythm amplitude, measured by RA, increases as the central nervous system matures [3]. In the elderly, locomotion deficits reduce M10 rates, while poorer sleep efficiency increases L5 values [6]. This leads to a reduction in the amplitude value, as measured by the AMP variable defined previously (Fig. 1).

This nonparametric variable needs further study to gain a better understanding of its relationship with individuals' quality of life (Table 2). Carvalho-Bos et al. (2007) showed that RA is inversely correlated with functional difficulty, mood disorders and loss of social interaction [13]. Moreover, in a study assessing associations between cardiovascular diseases (CVDs) and rest-activity rhythm, subjects with CVDs displayed lower amplitude values than healthy individuals [28]. Individuals with higher AMP values performed better on cognitive function tests [17].

In summary, in this review we have essentially presented two ways of calculating rhythm amplitude, one normalized and the other one not. The advantage of normalization is that it allows comparison of results from different actimeter models. The discussion on L5 and M10 regarding daily calculation or calculation for the 24-h average profile also holds for RA. Hence, we propose that RA also be calculated in two ways: for each day (RAm) and for the average 24-h profile (RAmp). In the first case, the information reflects the amplitude for each day, while in the second, it is related to rhythm regularity. Because IS already quantifies irregularity, it may be preferred to use measures calculated for each day separately.

What do these variables tell us?

High IV values have been found in the elderly and in Alzheimer patients, suggesting that IV represents an increase in rhythm fragmentation [6,7,9] associated with degeneration in the circadian timing system that might represent a reduction in the number of peptide-expressing neurons in the SCN (Fig. 1). As a consequence, these individuals display less efficient sleep [11], leading to a reduction in cognitive performance [17]. In addition, high IV values are associated with lower M10 and IS values (Fig. 2). In a study conducted with Alzheimer patients in whom aerobic physical activity was applied for three mo, the fragmentation of the rest-activity rhythm decreased (Table 3) [15].

The rhythm stability measured by IS depends on exposure to the light/dark cycle, integrity of the retinohypothalamic tract system (RHT), the presence of social synchronizers and practice of physical activities (Fig. 1). Alzheimer patients showed low IS values, because, besides being exposed to less natural light, they suffer from retina and optical nerve degeneration [16,29,30]. Treatment with artificial light positively affects the increase in synchronization measured by IS (Table 3) [14]. IS reduction might be linked to difficulty in synchronization with social cues, as occurs in Asperger's syndrome and Parkinson patients [19,20]. There is an association between the amplitude of daily activity and IS (Fig. 2) [3,4].

The L5 variable is a measure of nocturnal activity and also corresponds to the capacity for maintaining consolidated rest. An increase in the L5 value reflects the presence of movement during the rest phase, indicating fragmented sleep disturbed by arousals. In the elderly and individuals with neurodegenerative diseases, in whom high L5 values are displayed, the difficulty maintaining a consolidated sleep episode is linked to degeneration in sleep and wakefulness regulating nuclei, and may also be influenced by functional alterations in the CTS (Fig. 1).

Activity intensity during wakefulness is influenced by different factors, including mesencephalic activation, and is also related to the CTS's ability to concentrate motor activity into a phase, besides motor system integrity (Fig. 1). Individuals with Alzheimer's who show a reduction in the cortical activation process and in CTS functionality have displayed lower M10 values [4,5,10,24]. However, elderly patients suffering a stroke with motor cortex compromise also showed lower M10 values than a control group (unpublished data). As shown in Fig. 2, the value of M10 is influenced by any change in motor activity.

It has been suggested that a lower amplitude of rest-activity rhythm may be associated with the presence of certain mental disorders, such as attention-deficit/hyperactivity disorder (ADHD) and Asperger's syndrome [20,31]. In degenerative diseases, such as Alzheimer's and Parkinson's, AMP or RA values worsen with disease severity, a finding that points to loss of rhythm consolidation [10,19]. There seems to be an environmental influence on the amplitude of rest-activity rhythm, since patients with the same disease, hospitalized in different institutions, had different RA values [5,32]. In a study that evaluated the influence of bright-light therapy on the rhythms of people with seasonal affective disorder (SAD), the researchers observed an increase in RA with an improvement in sleep efficiency after the therapy (Table 3) [38].

In general, studies show that the less stable and more fragmented an individual's rest-activity rhythm, the worse their health. In an effort to restore patients' quality of life, some studies have sought to highlight the effects of therapy with bright light or transcutaneous electrical nerve stimulation (TENS), and physical activity (Table 3). However, to date, limited effects have been shown with these strategies [14,15,33,34]. Therefore, it is necessary to conduct further studies exploring other treatments that may help these patients to adjust their rest-activity rhythm, albeit partially.

The use of variables based on the cosinor parameters fails to address some questions related to rest-activity rhythm such as fragmentation. With nonparametric variables, it is possible to infer the key characteristics of circadian rhythms: synchronization with a zeitgeber (IS), amplitude (M10, L5 and RA) and robustness or fragmentation (IV).

A two-process model of sleep regulation and nonparametric analyses

From a theoretical perspective, one could speculate how nonparametric variables fit in the model of two processes of sleep regulation. In such a model, two processes interact to regulate the sleep–wake cycle [39]. The first is called 'homeostatic' (process S) and is responsible for determining the propensity of the individual to sleep. During wakefulness the intensity of process S increases.

The second process is based on circadian rhythmicity (process C) and its influence on state changes varies throughout the day.

In our proposed model presented in Fig. 1, social effects, such as work and school schedules, can force the individual to remain awake, increasing the pressure of the homeostatic component. The level of motor activity, measured by M10, is also responsible for increasing this pressure, which explains the relationship between amplitude and the sleep efficiency [11] (Fig. 2) variable. The efficiency of the homeostatic component for maintaining sleep can be measured by variables L5 and IV. It is worth remembering that L5 is related to sleep efficiency and both variables are related to nighttime awakenings.

Process C is mainly influenced by the suprachiasmatic nucleus [39]. In the proposed model depicted in Fig. 1, the neuronal integrity in the SCN and its outputs change this regulation. The neuronal degeneration is responsible for nocturnal awakenings and daytime sleepiness. Studies in humans and animals show that with ageing there is a reduction in the number of peptide-expressing neurons in the SCN and that this reduction might be associated with sleep fragmentation. In old mice, SCN neurons exhibited less synchronized activity that generated an output of lower amplitude [40].

Sleep variables and nonparametric analysis

The relationship between sleep analyses and nonparametric variables can be discussed from the biological and mathematical points of view. The similarity in the way of calculating some variables can establish correlations and it is necessary to check these carefully. Biologically, the relationship between the variables is given by the influence of the circadian system on sleep regulation.

There is a clear mathematical relationship between IV and the index of sleep fragmentation, as well as IV and the number of nighttime awakenings. Both sleep variables are related to changes in motor activity during sleep, and due to a mathematical relationship, the higher their values, the higher the IV values. When total sleep time and sleep efficiency are reduced there may be an increase in daytime sleepiness resulting in naps, which increase the value of IV.

Investigation of some disorders revealed that patients with bipolar disorder showed no more sleep fragmentation than the control group [18]. However, these patients showed greater fragmentation patterns of activity and rest, suggesting that this group has a less consolidated wakefulness. In older people, the number of naps and amount of sleep fragmentation increase, thereby raising the value of IV in this group [6]. Adults with ADHD showed lower sleep efficiency than control subjects, responsible for further fragmentation of their rhythm [31]. In the case of adults with Asperger's syndrome, there is no obvious fragmentation of the rest-activity rhythm, but this group had greater sleep fragmentation than the control group [20]. In this case, average IV was higher, but the difference did not reach significance. This result can be explained by the fact that both groups showed a more consistent wakefulness.

The sleep variables are not directly mathematically related to IS, but to the variability of a sleep variable, expressed by its standard deviation. This kind of analysis yields a result that indicates how regular the sleep pattern is, by means of a day-by-day comparison. An example of IS variation related to a disorder is a study in which lower IS values were found in adults with Asperger's syndrome when compared to a control group [20]. This group also showed a greater deviation in the variables of total sleep duration, sleep efficiency and sleep fragmentation.

Mathematically, there is no relationship between sleep and the M10 value, since M10 represents the most active time during the day. However, biologically, a shortened, fragmented and inefficient sleep impacts the value of M10. Studies have shown the existence of daytime sleepiness in people with poor sleep, and this may reduce the values of M10.

The L5 variable is related to the stage of sleep, thus an increase in the number of nocturnal awakenings and in the sleep fragmentation index raises the value of this variable. With ageing, there is an increase in fragmentation concomitantly with reduced sleep efficiency, and this leads to an increase in the L5 values [6].

The relative amplitude is related to M10 and L5 and therefore high levels of arousals and sleep fragmentation index increase the value of L5 and reduce the value of M10, as previously discussed. Thus, we conclude that disturbances during sleep are accompanied by a reduction in the value of relative amplitude.

In summary, the use of nonparametric analysis in actimetry seems to represent a good alternative for describing and comparing rest-activity rhythms, allowing inference of essential properties of circadian rhythms, such as synchronization with a zeitgeber, its amplitude and robustness. As shown in this paper, changes in these nonparametric variables reflect the severity of some neurological diseases. In the near future, this analysis could be incorporated into clinical practice and help to clarify the boundaries between healthy status and diagnoses of specific diseases.

Practice points

Nonparametric variables may be useful for:

1. understanding the behavior of a rhythm that does not follow a sinusoidal function;
2. identifying the fragmentation of a rhythm;
3. estimating the stability of a rhythm.

Research agenda

1. To work on an international standard for registration systems of rest-activity rhythm;
2. to improve analyses according to the development of data collection equipment, taking into account small epoch intervals;
3. to establish normative data for nonparametric variables according to different ages, gender and chronotype, which would allow their clinical use.

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